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Docket No.: PF-0339-2 CPA

Response Under 37 C.F.R. 1.116 - Expedited Procedure

Examining Group-1646

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By: _____ Printed: D. Ellis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#25
D.J
9/12/02

In re Application of: Bandman et al.

Title: NEW HUMAN INTEGRAL MEMBRANE PROTEIN

Serial No.:	09/265,710	Filing Date:	March 9, 1999
Examiner:	Ulm, J.D.	Group Art Unit:	1646

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Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed August 2, 2002, and received at the Patent Office on August 7, 2002, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $320 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, 12, 21, 42-45, and 48-51 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 8887, Frame 0894) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 2, 12, 21, 42-45, and 48-51
Claims allowed:	none
Claims canceled:	Claims 3-11, 13-20, and 22-41
Claims withdrawn:	Claims 46, 47, and 52-57
Claims on Appeal:	Claims 1, 2, 12, 21, 42-45, and 48-51 (A copy of the claims on appeal, as amended, can be found in the attached Appendix.)

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments were submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polypeptides, human integral membrane protein NIMPH, comprising the amino acid sequence of SEQ ID NO:1 (Specification, e.g., at page 2, lines 22-24; and page 13, lines 5-8 and 15-16). Appellants' invention also includes polypeptides having at least 90% or at least 95% identity to SEQ ID NO:1 (e.g., at page 13, lines 25-29), immunogenic fragments of a polypeptide of SEQ ID NO:1 (e.g., at page 27, lines 12-18), and compositions comprising a polypeptide of SEQ ID NO:1 (e.g., at page 31, lines 7-11).

NIMPH has strong chemical and structural homology with E25AMM from mouse (GenBank ID 624778; SEQ ID NO:3) (Specification, e.g., at page 13, lines 18-20). In particular, NIMPH and mouse E25AMM share 34% identity (e.g., at page 13, line 20; and Figure 2). In addition:

> "NIMPH is 266 amino acids in length and has one potential glycosylation site at N168; nine potential phosphorylation sites at S30, S49, T110, K119, K186, S208, T226, R231, and T234; and a prenylation site at C263. . . Northern analysis reveals the expression of this sequence in various libraries, at least 46% of which are immortalized

> or cancerous, at least 21% involve immune response, and at least 16% involve fetal/infant tissues. Of particular note is the expression of NIMPH in neuronal (28%) and gastrointestinal (19%) tissues." (Specification at page 13, lines 16-24)

The polypeptides of the present invention are useful, for example, for toxicology testing, drug discovery, and disease diagnosis.

(6) THE REJECTIONS

Claims 1, 2, 12, 21, 42-45, and 48-51 stand rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention is not supported by either a credible, substantial, and specific asserted utility or a well established utility (Office Action, May 7, 2002; page 2). Claims 1, 2, 12, 21, 42-45, and 48-51 also stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not enable one of skill in the art to use the claimed invention (Office Action, May 7, 2002; page 3). These rejections allege in particular that:

> "[t]oxicology testing is a general utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but it is not a specific utility with respect to SEQ ID NO:1 because the consequences of denaturing that particular protein are not disclosed, and toxicology testing does not constitute a 'well-established' utility." (Office Action, August 16, 2001; page 5)

and

> "[e]ven if the expression of Applicant's individual polypeptide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art." (Office Action, August 16, 2001; page 6)

Claims 2, 21, 42, 44, 45, 48, 50, and 51 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection alleges in particular that:

> "if one were presented with an isolated protein having an amino acid sequence which is at least 90% identical to SEQ ID NO:1 of the instant application they would not be able to determine if it was encompassed by the instant claims by reviewing the

description of the claimed genus which is presented in the instant specification." (Office Action, May 7, 2002; page 3)

(7) ISSUES

1. Whether claims 1, 2, 12, 21, 42-45, and 48-51 meet the utility requirement of 35 U.S.C. § 101.

2. Whether claims 1, 2, 12, 21, 42-45, and 48-51 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, *i.e.*, would the Specification enable one of ordinary skill in the art to use the claimed sequences, *e.g.*, in toxicology testing, drug development, and the diagnosis of disease.

3. Whether claims 2, 21, 42, 44, 45, 48, 50, and 51 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

(8) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

Claims 2, 21, 42, 44, 45, 48, 50, and 51 are grouped together.

(9) APPELLANTS' ARGUMENTS

Issue 1 – Whether the claims on appeal meet the utility requirement of 35 U.S.C. § 101

The rejection of claims 1, 2, 12, 21, 42-45, and 48-51 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as a human integral membrane protein,

abbreviated as NIMPH, encompasses polypeptide sequences encoded by genes that are expressed in brain, neuronal, gastrointestinal, cancerous, fetal/infant, and immune response-related tissues of humans (Specification, e.g., at page 13, lines 5-8 and 20-24; and page 25, lines 8-9). The novel polypeptide NIMPH is demonstrated in the specification to be a member of the class of integral membrane proteins (e.g., at page 13, lines 15-20). As such, the claimed polypeptide has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the claimed polypeptides actually function. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the claimed polypeptide is a member of the integral membrane protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Appellants submit with this brief the declaration of Lars Michael Furness (of record; originally submitted on February 19, 2002) describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of filing of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate. (Furness Declaration at ¶ 10).

The Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Examiner contends that the polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the

precise function of the protein. The uses of the claimed polypeptide for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise function.

The Examiner further asserts that the asserted utility of the claimed polypeptide in toxicology testing "is neither a specific or substantial utility" because that "would be comparable to conceding that any object of fixed mass has *prima facie* utility as a weight standard, irrespective of any other properties possessed by that object" (Office Action, August 16, 2001; pages 6-7). This is an inaccurate analogy. For utility as a weight standard, an object need only have the property of having a fixed mass. Any object having that same fixed mass could be used in place of that weight standard. The results of using any weight standard having that one particular property (i.e., a particular fixed mass) would be the same. For utility in toxicology testing, every distinct polypeptide expressed in humans **does** have utility based solely on the property of being expressed in humans. However, the results obtained from using any particular human-expressed polypeptide in toxicology testing is **specific to both the compound being tested and the polypeptide used in the test**. No two human-expressed polypeptides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides will differ depending on the identities of the compound tested and the two polypeptides. Therefore, the asserted utility of the claimed polypeptide for toxicology testing is specific and substantial, and more than adequately satisfies the statutory requirements for utility.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to

the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The use of a polypeptide in protein expression applications, including the techniques of two-dimensional polyacrylamide gel electrophoresis and western blot analysis, for drug development and toxicity testing, are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this brief. Objective evidence, not considered by the Examiner, further corroborates the credibility of the asserted utilities.

A. The membership of the claimed polypeptide in the integral membrane protein family demonstrates utility

Because there is a substantial likelihood that the claimed NIMPH polypeptide is a member of the family of polypeptides known as integral membrane proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as NIMPH in that application. Appellants have demonstrated by more than reasonable probability that NIMPH is a member of the integral membrane proteins family.

The Examiner must accept the Appellants' demonstration that the claimed polypeptide is a member of the integral membrane proteins family and that utility is proven by a reasonable probability unless it can be demonstrated through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288

(CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the integral membrane proteins family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must, like the other members of the integral membrane proteins family, be useful.

B. The uses of the claimed polypeptide for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to, Bandman et al. (U.S. Ser. No. 08/892,690, filed July 14, 1997), having the identical specification (hereinafter "the Bandman '690 application"). In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the application at issue (U.S. Ser. No. 09/265,710) on July 14, 1997 (the filing date of the Bandman '690 application) would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a

drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Declaration at ¶ 10.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states of tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Bandman '690 application . . . and other related pre-July 1997 publications, persons skilled in the art on July 14, 1997 clearly would have understood the Bandman '690 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity. . . (Furness Declaration, page 8, ¶ 10)

> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancers and neurological and immune disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, page 10, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before July 1997. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, form the basis of two-dimensional gel databases. (Wilkins at p. 26, Furness Declaration at Tab C).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Mr. Furness in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7): 655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-113:467 (2000).

The more genes -- and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The

implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequences and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the claimed polypeptide, the databases become even more

powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "substantial and specific" utilities (Office Action, August 16, 2001; page 6). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polypeptide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed polypeptide, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use either of the claimed polypeptides by themselves or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low.

Juicy Whip, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any polypeptide invention, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. The uses of NIMPH in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., at pp. 34-35), drug screening (e.g., at pp. 41-42), etc.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21,

1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of

utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

Broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Montedison,* 664 F.2d at 374-375.

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. Thus the Training Materials cannot be applied consistently with the law.

Issue 2 – Whether the claims on appeal meet the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to the "utility" issue

To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Issue 3 – Whether claims 2, 21, 42, 44, 45, 48, 50, and 51 meet the written description requirement of 35 U.S.C. § 112, first paragraph

Claims 2, 21, 42, 44, 45, 48, 50, and 51 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being based on a specification which provides an inadequate written description of what is claimed. The Examiner asserts that "if one were presented with an isolated protein having an amino acid sequence which is at least 90% identical to SEQ ID NO:1 of the instant application they would not be able to determine if it was encompassed by the instant claims by reviewing the description of the claimed genus which is presented in the instant specification" (Office Action, May 7, 2002; page 3). This rejection is traversed.

The requirement necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every

nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The subject matter encompassed by claims 2, 21, 42, 44, 45, 48, 50, and 51 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 42 recites polypeptides "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing and Figure 1. Variants of SEQ ID NO:1 are described in the specification at, for example, page 5, lines 15-18; page 6, lines 19-22; page 12, line 24 to page 13, line 2; and page 13, lines 25-29. One of ordinary skill in the art would recognize polypeptide sequences which are variants having at least 90%, or at least 95%, amino acid sequence identity to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art recognize whether it was a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited variants of SEQ ID NO:1.

The Examiner contends that an adequate written description has not been provided by stating that "[o]f the tens of thousands of material embodiments of proteins encompassed by the limitation 'polypeptide having at least 90% amino acid sequence identity to SEQ ID NO:1', only a tiny percentage would also be expected meet to limitation 'naturally occurring polypeptide'. Because the instant specification does not describe that structural feature or combination of features which distinguishes a polypeptide which meets both of these limitations from a polypeptide which meets only the first limitation, the instant specification does not provide an adequate written description of the claimed genus of polypeptide" (Office Action, May 7, 2002; pages 3-4 at § 7). The Examiner ignores the fact that Appellants **have** provided the combination of features which "distinguishes a polypeptide which meets both of these limitations." The combination of features are recited, for example, in the

claims. For example, independent claim 2 recites that the claimed polypeptides have the biological feature of being "naturally occurring" polypeptides, combined with the structural feature of "having at least 90% amino acid identity to SEQ ID NO:1." By reciting this combination of biological and structural features, an adequate written description of the claimed subject matter has been provided.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claim 2 recites chemical structure to define the claimed genus:

> 2. A substantially purified, naturally occurring polypeptide having at least 90% amino acid identity to SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polypeptides which are integral membrane proteins, including polypeptides which are integral membrane proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as integral membrane proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% [or at least 95%] identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 266 amino acid residues). This variation is far less than that of all potential integral membrane proteins related to SEQ ID NO:1, i.e., those integral membrane proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial

No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 14, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Examiner failed to base his written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be overturned.

(10) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The written description rejection should also be reversed, based on at least the arguments presented above.

Due to the urgency of this matter, and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

Respectfully submitted,

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Date: August 29, 2002.

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APPENDIX

Claims on appeal:

1. A substantially purified human integral membrane protein comprising the amino acid sequence of SEQ ID NO:1.

2. A substantially purified, naturally occurring polypeptide having at least 90% amino acid identity to SEQ ID NO:1.

12. A composition comprising the protein of claim 1 and a suitable pharmaceutical carrier.

21. A purified polypeptide of claim 42 comprising an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

42. An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, and

c) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

43. An isolated polypeptide of claim 42 comprising the amino acid sequence of SEQ ID NO:1.

44. An isolated polypeptide of claim 42 comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

45. An isolated polypeptide of claim 42 comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1.

48. A composition comprising a polypeptide of claim 42 and a pharmaceutically acceptable excipient.

49. A composition comprising a polypeptide of claim 43 and a pharmaceutically acceptable excipient.

50. A composition comprising a polypeptide of claim 44 and a pharmaceutically acceptable excipient.

51. A composition comprising a polypeptide of claim 45 and a pharmaceutically acceptable excipient.